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Dated 9 May 2000

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Request for grant of a patent

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The Patent Office
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1. Your reference — KR/JW/P32310

2. Patent ap[illegible]
(The Patent **9912196.4** — 25 MAY 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   Patents ADP number *(if you know it)*

   If the applicant is a corporate body, give the country/state of its incorporation

   SmithKline Beecham plc
   New Horizons Court, Brentford, Middx TW8 9EP,
   Great Britain

   58 00974 002

4. Title of the invention — Novel Pharmaceutical

5. Name of your agent *(if you have one)*

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   Patents ADP number *(if you know it)*

   CORPORATE INTELLECTUAL PROPERTY

   SMITHKLINE BEECHAM PLC
   TWO NEW HORIZONS COURT
   BRENTFORD
   MIDDLESEX TW8 9EP

   58 00974 004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is named as an applicant, or
   c) any named applicant is a corporate body
   See note (d)

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	10
Claim(s)	
Abstract	
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 1/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature K Rutter Date 25-May-99

K Rutter

12. Name and daytime telephone number of person to contact in the United Kingdom

K Rutter 01279 644396

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NOVEL PHARMACEUTICAL

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

International Patent Application, Publication Number WO94/05659 discloses certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activity including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)").

It has now been discovered that Compound (I) exists in a novel polymorphic form which is particularly suitable for bulk preparation and handling. The novel form can be prepared by an efficient, economic and reproducible process particularly suited to large scale preparation.

The novel polymorphic form ('the Polymorph') also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides a polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt characterised in that it provides:

(i) an infrared spectrum substantially in accordance with Figure I;

(ii) a Raman spectrum substantially in accordance with Figure II; and /or

(iii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure III.

The present invention encompasses the Polymorph isolated in pure form or when admixed with other materials, for example the known forms of Compound I or any other material.

Thus in one aspect there is provided the Polymorph in isolated form.

In a further aspect there is provided the Polymorph in pure form.

In yet a further aspect there is provided the Polymorph in crystalline form.

The invention also provides a process for preparing the Polymorph, characterised in that Compound (I) is suspended in acetone under nitrogen and stirred at reflux for an extended period of time, for example 17 hours after which time the Polymorph is isolated from the reaction mixture. In an alternative process a solution of Compound (I) in denatured ethanol at an elevated temperature, for example 50°C, is seeded with the Polymorph then cooled to 20-25°C to provide the Polymorph, after which time the Polymorph is recovered from the denatured ethanol. The solution of Compound (I) in the denatured ethanol is conveniently prepared by dissolving

Compound (I) in the required amount of denatured ethanol at an elevated temperature for example 60°C.

Typically the Polymorph is recovered from the reaction by filtration and subsequent drying, usually at an elevated temperature, for example 50°C.

In a further aspect, the invention provides a process for converting Polymorph to Compound (I), wherein a solution of Polymorph in a suitable solvent, such as acetone or ethanol, is seeded with Compound (I). Generally, the solution of Polymorph is obtained by dissolving Polymorph at an elevated temperature in the solvent, such as acetone or ethanol.

Compound (I) is prepared according to known procedures, such as those disclosed in WO94/05659. The disclosures of WO94/05659 are incorporated herein by reference.

When used herein "denatured ethanol" means ethanol containing small amounts of methanol for example ethanol containing 4%v/v of methanol.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating ,such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly the Polymorph for use as an active therapeutic substance.

More particularly, the present invention provides the Polymorph for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The Polymorph may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of the Polymorph and dosages thereof are generally as disclosed for Compound (I) in International Patent Application, Publication Number WO94/05659.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Polymorph and a pharmaceutically acceptable carrier therefor.

The Polymorph is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose,

carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or ,prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Polymorph to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Polymorph may be taken in doses, such as those described above.

Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

In a further aspect the present invention provides the use of the Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following example illustrates the invention but do not limit it in any way.

Example 1: Preparation of Polymorph
Compound (I) (8.0 g) was suspended in acetone (80 ml) under nitrogen and the resulting slurry was stirred at reflux for 17.5 h. The mixture was then cooled to ambient and stirred for 30 min. The product was isolated by filtration, washed with acetone and dried *in vacuo* at 50°C to give 6.9 g (86%) of the Polymorph.

Example 2: Conversion of Polymorph to Compound (I)
Polymorph (18.0 g) was added to acetone (450 ml) and the resultant mixture was heated at reflux under nitrogen for 30 min. The hot solution was filtered, and the filtered solution was concentrated by distillation at atmospheric pressure (270 ml of acetone was collected). The concentrated solution was then allowed to cool at about 1°C/min and at 50°C the solution was seeded with Compound (I) (0.09 g). Cooling at about 1°C /min was continued. The resulting slurry was stirred for 1 h at ambient temperature, then the solid was isolated by filtration, washed with acetone and dried *in vacuo* at 50°C to give 15.1 g (84%) of Compound (I).

Example 3: Conversion of Polymorph to Compound (I)
A mixture of Polymorph (10.0 g) in denatured ethanol (90 ml) was heated under nitrogen to give a clear solution. The clear solution was stirred at 62°C for 30 min then filtered hot to a vessel preheated to 55°C. The filter was washed with hot denatured ethanol (10 ml). The temperature of the filtrate was adjusted to 60°C before cooling, with stirring, at about 1/min. The cooling mixture was seeded at 52°C with Compound (I) (0.4 g) and cooling at 1°C/min with stirring was continued. The resultant slurry was stirred at ambient temperature for 1 h and the solid was isolated by filtration, washed with denatured ethanol and dried *in vacuo* at 50°C to give 8.4 g (84%) of Compound (I).

Charaterising data

Infrared
The infrared absorption spectrum of a mineral oil dispersion of the Polymorph was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm^{-1} resolution. Data were digitised at 1 cm^{-1} intervals. The spectrum obtained is shown in Figure I.

Raman
The Raman spectrum of the Polymorph was recorded through a glass vial using a Perkin Elmer 2000R spectrometer at 4 cm^{-1} resolution and is shown in Figure II. Excitation was achieved using a Nd:YAG laser (1064 nm) with a power output of 500 mW.

X-Ray Powder Diffraction (XRPD)

The XRPD pattern of the Polymorph is shown in Figure III and a summary of the XRPD angles and calculated lattice spacings characteristic of the Polymorph is given in Table I.

A Bruker AXS D8 Advance X-ray powder diffractometer (Cu X-ray source) was used to generate the pattern using the following acquisition conditions:

Tube anode:	Cu
Generator tension:	40 kV
Generator current:	40 mA
Start angle:	2.0 °2θ
End angle:	35.0 °2θ
Step size:	0.02 °2θ
Time per step:	2.5s

Figure 1: Infrared Spectrum of the Polymorph

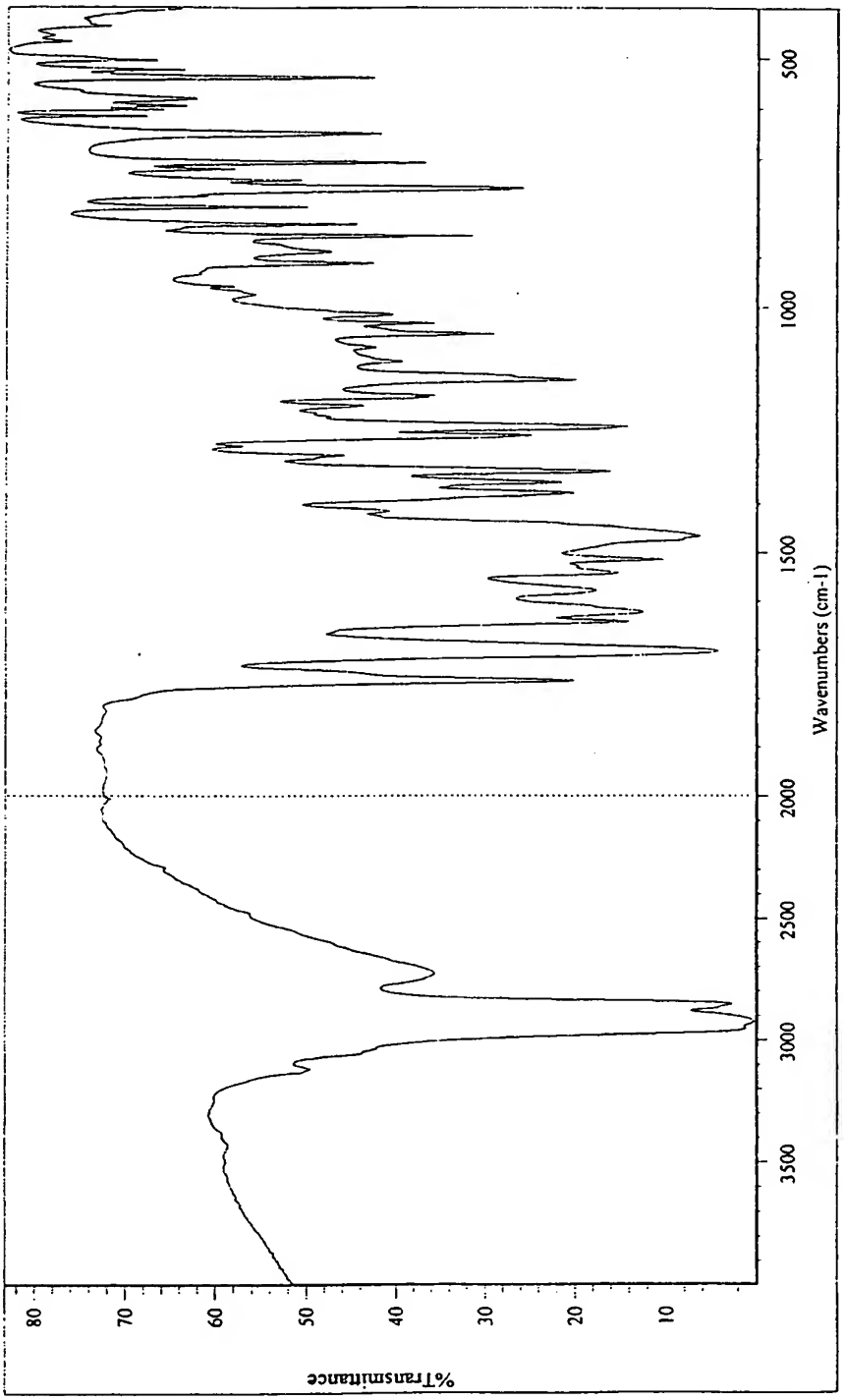


Figure II: Raman Spectrum of the Polymorph

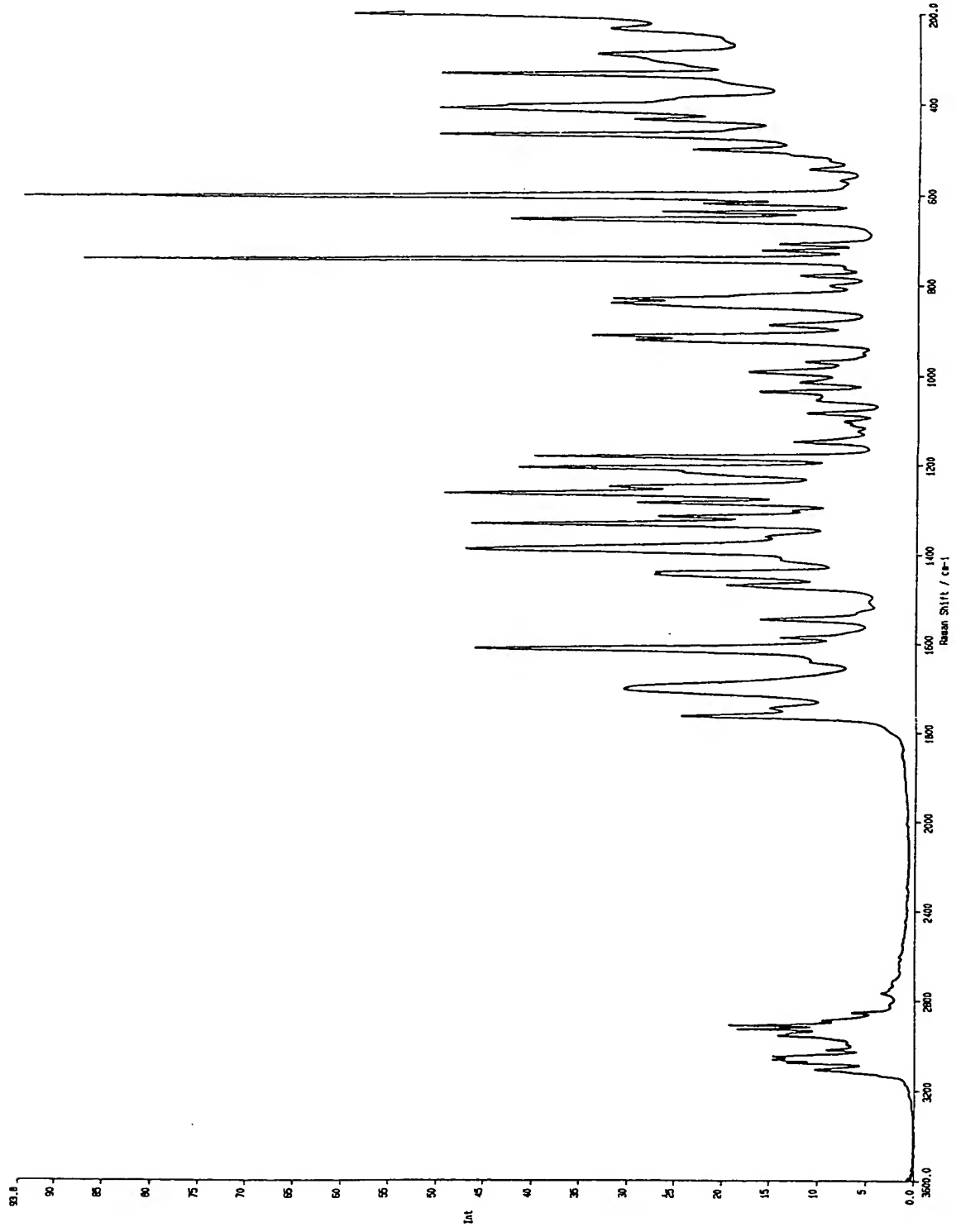
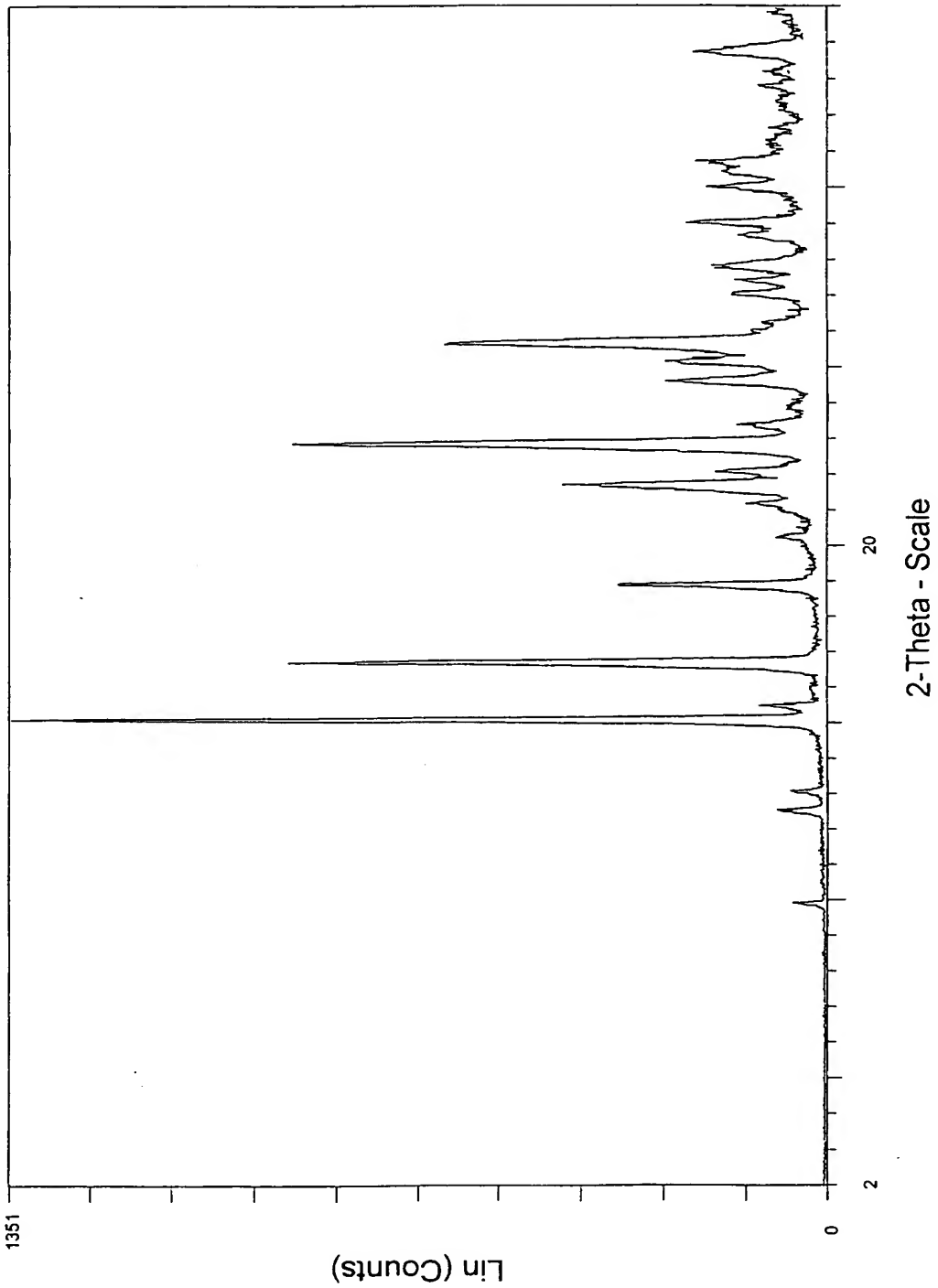


Fig III: X-Ray Powder Diffraction Pattern of the Polymorph



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